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08/377,798

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
PRIPUTNIEV, I	
ART UNIT	**PAPER NUMBER**
1806	5

HELEN GREER
WOLF GREENFIELD & SACKS
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON MA 02210-2211

DATE MAILED: 10/13/95

This is a communication from the examiner in charge of your application.
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☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 0 month(s), 30 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-38 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☐ Claims _____ are rejected.

5. ☐ Claims _____ are objected to.

6. ☒ Claims 1-38 are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2-93)

The Group Art Unit assignment of this application is different from that of the parent application. To aid in association of papers with the file, it is requested that any future communications from Applicant reference Art Unit 1211.

The Examiner notes that parent case 08/253,663 is now abandoned, and requests that the first paragraph of the specification be amended to indicate this fact.

Applicant's election with traverse of Species C in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the species were improperly described by the Examiner ("inhibitor" in place of "ligand") and that the species are not mutually exclusive. This is found to be persuasive in part.

It appears that Applicant is correct in that the word "inhibitor" in the listing of Species A, B, and E, should have been "ligand". However, this is not a convincing reason for traversal of the requirement because despite the misused word, it was entirely clear which embodiments of the invention were intended to be encompassed by each of Species A-E.

Because a sulfatide (Species D) is a carbohydrate, and because "analogs" (Species E) could encompass carbohydrates, these species will be included in the instant examination on the merits.

Applicant's argument that the glycoproteins are not mutually exclusive species from the carbohydrates is not convincing. Although a particular glycoprotein may include, for example, the same saccharide moiety as a particular carbohydrate, the two are still distinct chemical entities and therefore mutually exclusive.

The requirement, as modified, is still deemed proper and is therefore made FINAL. To summarize, claims 1-13, 19, 20, and 23-38 will be examined insofar as they read on carbohydrates which do not contain protein or peptide moieties.

Claims 1-13, 19, 20, 23-31 and 35-38 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims which do not read on prevention of atherosclerosis. A worker of skill in this art would have been faced with an undue burden of experimentation in order to determine how to "prevent" atherosclerosis. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The factors to be considered in determining what constitutes undue experimentation were set forth by the court in *Ex parte Forman* (230 USPQ 546 (1986)). These factors are the quantity of experimentation; the amount of direction or guidance presented in the specification; the presence or absence of working examples; the nature of the invention; the state of the prior art; the level of skill of those in the art; predictability or unpredictability of the art; and the breadth of the claims.

Much is understood about the mechanisms leading to atherosclerosis, and a number of methods of treating it are widely employed. See, for example, the last paragraph in column 1 on page 808 of ROSS (AF). However, "prevention" of atherosclerosis reads on preclusion of any development whatsoever of the fatty streak. This early form of atherosclerosis (see ROSS, first full paragraph in column 2 on page 801) occurs widely even in persons who are apparently healthy and have no family history of atherosclerotic disease, including young children. No examples have been presented to teach the worker of skill in this art how to prevent atherosclerosis. It is apparent that the enabled treatment aspects of the invention do not also enable the prevention aspects, because while the art recognizes how to treat atherosclerosis, it has not yet developed any effective means of preventing it. For these reasons, it is concluded that the worker of ordinary skill in the art would have been faced with an undue burden of experimentation in order to use the invention for prevention of atherosclerosis.

Claims 28-31 are included in this rejection insofar as the intended meaning of "partially prevent" is unclear. See the rejection under 35 U.S.C. § 112, second paragraph.

Claims 28-31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point

out and distinctly claim the subject matter which Applicant regards as the invention.

The claims are indefinite as to the intended meaning of "partially prevent". The term "prevent" implies a total lack of something, and it is unclear how this can happen to a "partial" extent. If adequate support, either literal or implied, is available in the specification, Applicant may wish to consider replacing "prevent" with --inhibit--.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-13, 19, 20, and 23-38 are rejected under 35 U.S.C. § 103 as being unpatentable over KOGAN *et al.* (A), RAO *et al.* (B), or SEEKAMP *et al.* (K), in view of ROSS (AF).

Applicant claims a method of treating or preventing atherosclerosis in a mammal comprising administration of an agent which inhibits binding of P-selectin to a ligand. In accordance with the restriction requirement, the agent is a carbohydrate which does not contain peptide or protein moieties. The inhibitory agent may be a portion of P-selectin or a ligand thereof, including sialyl-Lewis x, sialyl-Lewis a, and their analogs.

Each of KOGAN, RAO, and SEEKAMP teaches oligosaccharides or their derivatives which may be used to block interaction of P-selectin with its ligands, and that such blocking is useful for treatment of certain cardiovascular disorders. See the Abstracts of KOGAN and SEEKAMP. See the Abstract and claim 1 of RAO. KOGAN and SEEKAMP further disclose that the oligosaccharides may be

derivatives of sialyl-Lewis x or sialyl-Lewis a. KOGAN clarifies (Abstract, lines 1-3) that sialyl-Lewis x and sialyl-Lewis a are themselves ligands of P-selectin, and that they are found on cell surfaces. KOGAN further states that the oligosaccharide compounds are useful for inhibition of granular release, as in instant claim 26; see column 2, second full paragraph, for example. SEEKAMP and RAO also teach that the cell may be an endothelial cell, and that the ligand may be on a leukocyte such as a neutrophil; see SEEKAMP, first full paragraph, column 2, page 592, and RAO, column 8, lines 9-13). Each of the references indicates that the oligosaccharides disclosed inhibit the binding of molecules which are necessary for the function of P-selectin, as recited in claim 27. None of KOGAN, RAO, or SEEKAMP teaches that blocking the interaction of P-selectin with its ligands is useful specifically for treatment or prevention of atherosclerosis.

The ROSS reference is a review article which provides a thorough overview of the pathogenesis of atherosclerosis. ROSS confirms that the prior art had recognized the role of adhesion molecules such as selectins in atherogenesis. See, for example, the first full paragraph on page 805. The Examiner notes that ELAM is a selectin. ROSS also states that the adhesion molecules may be on the surface of endothelial cells, and that the ligands may be on monocytes; see the first full paragraph on page 805. ROSS provides a description of the role of platelets in atherosclerosis, and

suggests that inhibition of platelets is a means of treating atherosclerosis; see the first full paragraph on page 807. ROSS also describes the various stages of atherosclerosis as set forth in instant claims 28-36.

It would have been obvious for a person of ordinary skill in the art at the time of the invention to employ oligosaccharides such as derivatives of sialyl-Lewis x or sialyl-Lewis in a method of treatment or prevention of atherosclerosis, wherein the method is based on blocking the interaction of P-selectin with its ligands. The primary references had taught that such oligosaccharides could be used in treatment of highly related cardiovascular disorders by virtue of their inhibitory activity. This in itself would have motivated the ordinarily skilled artisan to treat atherosclerosis in a similar manner. The teaching of ROSS had specifically disclosed the link between atherosclerosis and cell adhesion molecules such as selectins, thereby providing one of ordinary skill in the art with a reasonable expectation of successful treatment of atherosclerosis by this method. Given that the oligosaccharides of the primary references are taught to bind to P-selectin, it is not seen that the specific identity of the ligand, as in instant claim 7, provides for any patentable distinction.

Claims 1-12, 19, 20, 26-38 are rejected under 35 U.S.C. § 103 as being unpatentable over ROHRER *et al.* (L) in view of DE-AMBROSI (C), if necessary further in view of ROSS (AF).

Applicant claims a method of treating or preventing atherosclerosis in a mammal comprising administration of an agent which inhibits binding of P-selectin to a ligand. In accordance with the restriction requirement, the agent is a carbohydrate which does not contain peptide or protein moieties. The inhibitory agent may be a portion of P-selectin or a ligand thereof, including heparin oligosaccharides.

ROHRER teaches that administration of heparin suppresses platelet granule secretion, and that this suppression occurs as a result of the ability of heparin to interfere with the interaction between platelets and GMP-140; see the Abstract. The Examiner notes that GMP-140 is also known as P-selectin. ROHRER clearly states that platelet degranulation is implicated in atherogenesis (Abstract, lines 1-2). ROHRER also suggests that heparin fragments could be advantageously employed in place of standard heparin; see the final sentence of the Abstract. ROHRER does not explicitly disclose treatment or prevention of atherosclerosis by administration of heparin.

DE-AMBROSI teaches a method of treatment of thrombosis and atherosclerosis by administration of heparin derivatives (see claim 7 of the reference), further implies that other heparins would be

expected to have similar therapeutic properties (see column 1, lines 21-30).

It would have been obvious for a person of ordinary skill in the art at the time of the invention to use heparin or its derivatives in a method of treatment or prevention of atherosclerosis, wherein the method requires inhibition of the interaction between P-selectin and its ligand. The ordinarily skilled worker would have been motivated to do so by ROHRER's disclosure that heparin could interfere in a process known to be associated with atherosclerosis, coupled with the teaching of DE-AMBROSI of a method of treatment of atherosclerosis based on administration of heparin derivatives. If further motivation is needed, it is provided by ROSS's detailed description of the nature of the molecular interactions which lead to atherosclerosis. The comments set forth above with regard to ROSS also apply to the instant rejection. It is not seen that the specific identity of the ligand (instant claim 7), or the source from which the agent is derived (instant claim 25) provides for any patentable distinction.

No claim is allowed.

The following references are cited to indicate the current state of the art more fully: Nicolson *et al.* (D), Medford *et al.* (E), Roux *et al.* (M), Yao *et al.* (N), and Buja (O).

Papers relating to this application may be submitted to Group 1200 by facsimile transmission. The number of the fax machine for official papers in Group 1200 is (703) 308-4556. The cover sheet of any document submitted by facsimile transmission should be clearly marked as either an official or an informal communication.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kathleen Kahler Fonda, at telephone number (703) 308-1620. Examiner Fonda can generally be reached from Monday through Thursday, as well as on alternate Fridays, between 7:30 a.m. and 5:00 p.m. If the Examiner cannot be reached, questions may be addressed to Supervisory Patent Examiner John Kight, at (703) 308-0204. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1200 receptionist whose telephone number is (703) 308-1235.

KKF

Kathleen Kahler Fonda, Ph.D.

Gary L. Kunz

GARY L. KUNZ
PRIMARY EXAMINER
GROUP 1200